

Serum monoclonal immunoglobulins in childhood

FRANÇOISE DANON and MAXIME SELIGMANN

From the Department of Immunochemistry, Research Institute on Blood Diseases, Hôpital Saint-Louis, Paris, France

Danon, F., and Seligmann, M. (1973). *Archives of Disease in Childhood*, **48**, 207.

Serum monoclonal immunoglobulins in childhood. Of 18 children with monoclonal immunoglobulins in their sera, 13 had a primary or secondary immunodeficiency. The monoclonal immunoglobulin belonged to each of the three main Ig classes, and in 3 children multiple monoclonal components were detected. The level of the monoclonal component exceeded 0.5 g/100 ml in 7 cases. The monoclonal immunoglobulin disappeared spontaneously in 9 children. The significance of this homogeneous component and the importance of the underlying immunodeficiency are outlined.

Monoclonal immunoglobulins (Ig) are mainly associated with multiple myeloma and Waldenström's macroglobulinaemia. However, during recent years several reports have been published concerning monoclonal Ig without evidence of such haematological diseases (Osserman and Takatsuki, 1965; Hallen, 1967; Hobbs, 1967; Danon, Clauvel, and Seligmann, 1967; Michaux and Heremans, 1969). These Ig abnormalities, with or without clinical manifestations, have usually been detected in adults and elderly people, but monoclonal Ig have occasionally been reported in childhood. The present report concerns 18 children; we show that in childhood monoclonal Ig is most often associated with primary or secondary immunodeficiency and that it may disappear spontaneously.

Material and methods

Seventy-three serum samples from 18 children were studied by electrophoresis and immunoelectrophoresis. Most of the children were being followed in our clinic on account of haematological or immunological diseases, and were submitted to a systematic Ig survey. In a few a sudden increase in the erythrocytic sedimentation rate sometimes provided stimulus to perform immunoelectrophoretic analysis.

Electrophoresis was performed in 1% agar gel, the proteins being stained with amidoblack, and in cellulose acetate, the level of the homogeneous components being estimated as a percentage of the total uptake of ponceau red. Immunoelectrophoretic analysis was carried out in barbitalone buffer pH 8.2, ionic strength 0.05, with a variety of rabbit antisera prepared in our laboratory and conveniently absorbed, including antisera specific for γ , μ , α , δ , κ , and λ chains.

Quantitation of the immunoglobulin classes not

including the monoclonal components was performed by radial diffusion in agar with specific antisera incorporated into the gel (Mancini, Carbonara, and Heremans, 1965). Antinuclear antibodies were sought by the indirect immunofluorescence technique on liver sections. Antibodies to human and rabbit γ -globulin were detected by the latex F II and Waaler Rose reactions.

Our criteria for defining a population of Ig molecules as 'monoclonal' were (1) an abnormal bow reacting with antisera corresponding to only one type of heavy and light chain on immunoelectrophoresis; (2) a discrete homogeneous peak with sharp borders migrating by electrophoresis in the same region as the immunoelectrophoretic bow. Both criteria were fulfilled in 14 of 18 cases. In the other cases, the monoclonal Ig level was not sufficient to induce a sharp peak but the light chain typing, either by immunoelectrophoresis of the whole serum or after sucrose density gradient ultracentrifugation for IgM components confirmed its antigenic homogeneity.

We have excluded from this study two kinds of abnormalities. Firstly, we do not report here the cases with a monoclonal protein characteristic of the α -chain disease (Seligmann *et al.*, 1968) which occurs in young adults and children (Seligmann, Mihaesco, and Frangione, 1971). Secondly, we do not consider as monoclonal the IgG showing only a restricted cathodal electrophoretic mobility, which are often encountered in the sera of young children (Golebiowska and Rowe, 1967). In our own experience these IgG molecules with restricted electrophoretic heterogeneity always shared both κ - and λ -chains and could not therefore be considered as antigenically homogeneous.

The criterion for the disappearance of the monoclonal Ig was the failure to detect on subsequent sera homogeneous protein previously detectable by electrophoresis and/or immunoelectrophoresis (Danon and Seligmann, 1972).

TABLE
Main relevant

Case No.	Diagnosis	Immuno-suppressive therapy*	Age	Monoclonal Ig type (g/100 ml)		
					<0.5	>0.5≤1
1	Severe combined immunodeficiency		6 mth	Gκ + Gλ		+
2	Severe combined immunodeficiency		13 mth	Gλ	+	
3‡	Wiskott-Aldrich syndrome		5 mth	G		+
4	Wiskott-Aldrich syndrome		10 yr	Gλ	+	
5	Primary immunodeficiency		6 mth	Gκ + Gλ + Aλ		+
6	Possible immunodeficiency		14 mth	Gκ	+	
7	Lymphoblastic leukaemia	+	5 yr	Gκ		+
8	Lymphoblastic leukaemia	+	15 yr	Gλ	+	
9	Acute myeloblastic leukaemia	+	14 yr	G	+	
10	Myelomonocytic leukaemia	+	3 yr	Gκ		+
11	Subacute myeloblastic leukaemia	+	5 yr	Mκ	+	
12	Lymphoblastosarcoma	+	5 yr	Gκ	+	
13§	Subacute sclerosing panencephalitis	+	6 yr	Gλ + Gλ		+
14	Familial lymphohistiocytosis		8 yr	G	+	
15	Chromosomal abnormality		3 wk	M	+	
16	Chromosomal abnormality		2 yr	Aλ	+	
17	Schönlein-Henoch purpura and nephropathy		20 mth	Gκ		
18	Thrombotic thrombocytopenic purpura		14 yr	Gλ		+

*Before discovery of monoclonal Ig; ‡Interval between finding of monoclonal Ig and first electrophoresis or immunoelectrophoresis showing no

Results

The most important results are summarized in the Table.

Immunoglobulin findings. The monoclonal Ig belonged to any one of the three main Ig classes, while in 3 patients multiple monoclonal Ig were detected.

The level of the monoclonal Ig was over 0.5 g/100 ml in 7 cases and as high as 1 g/100 ml in 3 cases (Cases 5, 7, and 13 of the Table). The level of serum polyclonal Ig belonging to classes other than that of the monoclonal components was normal in 9, increased in 7, and decreased only in 2 cases. This finding was remarkable in several patients with immunodeficiency diseases.

Antinuclear factors were found in 5 of 16 cases with titres as high as 1/100 in 2 cases. No DNA antibodies were detected by complement fixation or precipitin tests. Rheumatoid factor was found in 3 sera. Two of these had both antinuclear and anti-γ-globulin antibodies.

The proteinuria was investigated in 6 patients. Two of them showed excretion of a very small amount of Bence-Jones protein, detectable only after urine concentration (Cases 5 and 10). The CSF was investigated in 2 patients (Cases 5 and 13), monoclonal IgG being found in both.

Clinical findings. The clinical diagnoses are summarized in the Table. It is noteworthy that at least 5 children suffered from a primary immuno-

deficiency. At the time of examination they had never received γ-globulin injections (nor thymus or marrow grafts). 6 children had leukaemia or lymphosarcoma, all receiving chemotherapy, and 4 being in complete remission. In 5 cases the monoclonal Ig was known not to be present at the time of diagnosis and appeared at a later stage, as shown by successive electrophoretic patterns. As a rule, these serial studies were performed at intervals of several weeks or months so that the precise time of monoclonal Ig appearance could not be ascertained except in the following case.

Case 7. This child was first seen in 1967 for an acute lymphoblastic leukaemia. A complete remission was induced. During the following three years he was under maintenance therapy with mercaptopurine and amethopterin, with reinductions at regular intervals with prednisone, vincristine, and rubidomycin. He was admitted to hospital in October 1970 for an unexplained fever (relapse of the leukaemia was excluded). The sedimentation rate was 25 mm in the first hour and the serum electrophoresis pattern was normal (Fig. (1)). 12 days later the sedimentation rate had risen to 160 mm and the serum protein electrophoresis revealed a discrete γ-peak (Fig. (2)). Immunoelectrophoresis showed a diffuse increase of IgM and IgG with a monoclonal κ IgG. Virological and serological investigations led to the diagnosis of cytomegalovirus infection. Cytomegalovirus antibodies reached a titre of 1/1600 and decreased thereafter.

data in the 18 cases

Other Ig classes	Antinuclear factor	Rheumatoid factor	Additional features	Disappearance of monoclonal Ig†
IgM ↗	—	—		
N ↘	—	—		
N ↘	ND	ND		2 mth
N ↘	—	—		
IgM ↗	+	+		1 yr
N ↘	—	—		
IgM ↗	—	—	Cytomegalovirus infection	1 yr
IgM ↗	+	—		
IgA: N ↘	+	—	Cytomegalovirus infection	2 mth
IgM ↗	+	+	Cytomegalovirus infection	15 dy
N ↘	+	—	Cytomegalovirus infection	4 dy
N ↘	—	+	Cytomegalovirus infection	8 mth
N ↘	—	—		
N ↘	ND	ND		
N ↘	—	—		
N ↘	—	—		2 mth
N ↘	—	—		2 mth

more such component; ‡Dalloz *et al.* (1965); §Loirat, Danon, and Broyer (1971). ND, not done; N, normal.

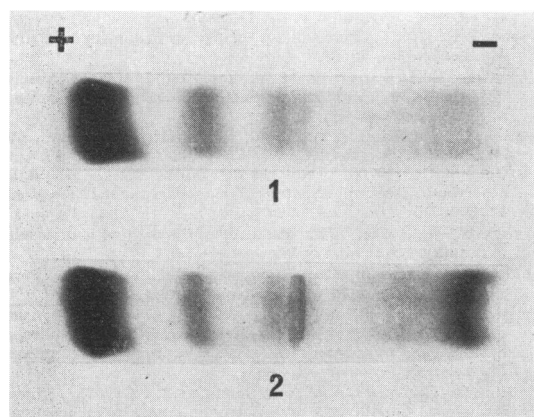


FIG.—Successive agar gel electrophoresis of the sera of Case 7 (lymphoblastic leukaemia): (1) 29 October 1970, (2) 11 November 1970.

The child recovered. The level of the monoclonal Ig slowly decreased and finally disappeared after 6 months.

Follow-up studies. We have never observed any increase in the level of the monoclonal Ig after initial detection, though many of the children could be followed for only a limited period, since 10 of them died from the underlying disease.

The main finding during the follow-up studies was the transience of the monoclonal Ig in 9 cases. In 7 of these children, its disappearance occurred

spontaneously (reported in detail elsewhere by Danon and Seligmann, 1972). As shown in the Table, the interval between its detection and disappearance varied between 4 days and 1 year.

Discussion

This report clearly shows that the occurrence of serum monoclonal Ig is not a very exceptional event during childhood and that such immunoglobulin abnormalities may be detected in very young infants as well as in older children. None of the 18 children reported in the present study was affected with myeloma or Waldenström's macroglobulinaemia, emphasizing that it is probably only α -chain disease which in childhood leads to a presumably malignant plasmacytic proliferation characterized by a monoclonal Ig (Irunberry *et al.*, 1970; Stoop *et al.*, 1971; Seligmann *et al.*, 1971).

As far as the associated diseases are concerned, the striking finding in the present study is that 13 of the 18 children were affected with primary or secondary immunodeficiency. The common diagnosis in the primary immunodeficiency group was either severe combined immunodeficiency or the Wiskott-Aldrich syndrome. Among the other patients, 7 were under immunosuppressive therapy when the monoclonal Ig was detected, most suffering from a malignant haematological disease.

Our findings may be partly related to the fact that our department is mainly devoted to haematology and immunology. However, most of the case reports documenting monoclonal Ig in childhood also

concern patients with immunodeficiency diseases: Wiskott-Aldrich syndrome (Radl *et al.*, 1967; Blaese *et al.*, 1971), ataxia telangiectasia (Cawley and Schenken, 1970), and severe combined immunodeficiency (Stoop, Ballieux, and Weyers, 1962; Schaller *et al.*, 1966; Becroft and Douglas, 1968). In these cases and in those reported here, the patients had received neither γ -globulin nor thymus or bone marrow grafts. In contrast, Harboe *et al.* (1966) and Radl *et al.* (1972) have also documented the appearance of monoclonal Ig after the grafting of lymphoid cells into infants affected with severe combined immunodeficiency.

The occurrence of monoclonal Ig associated with acute leukaemia has been reported by Stoop *et al.* (1968), Lindqvist, Ragab, and Osterland (1970) and Hitzig and Jako (1971). These 3 children, as well as our 5 were all treated by immunosuppressive therapy. One of our children (Case 12) was not affected with a malignant haematological disease but had been treated for 2 years by immunosuppressive therapy for a nephrotic syndrome: 3 months after withdrawal of treatment, a subacute sclerosing panencephalitis appeared and led to death 6 months later (Loirat *et al.*, 1971).

These data strongly suggest that the appearance of monoclonal Ig is favoured by an underlying immunodeficiency whether primary or secondary. Though a precise antibody activity of the homogeneous component has not been proven, it seems probable that monoclonal Ig in childhood often represents homogeneous antibodies similar to the antibodies of restricted heterogeneity elicited in man and rabbits by immunization with carbohydrate antigens (Krause, 1970). In several cases the appearance and detection of the monoclonal Ig coincided with a viral infection. Monoclonal Ig has recently been found in several newborns affected with congenital toxoplasmosis (C. Griscelli, G. Desmont, and D. Frommel, personal communication, 1972). It is of great interest that in half of our cases the monoclonal components were transient. This transient character is similar to the findings in rabbit immunized with streptococcal carbohydrates (Osterland *et al.*, 1966). Immunodeficiency could well be a predisposing factor for some antigenic stimuli to induce formation of uniform antibodies. This hypothesis is in accordance with previous findings in animals in which the immunological defects were induced experimentally (Humphrey, Parrot, and East, 1964; Pierce, Chubb, and Long, 1966).

REFERENCES

- Becroft, D. M. O., and Douglas, R. (1968). Thymic alymphoplasia monoclonal gammopathy, and *Pneumocystis Carinii* pneumonia in an infant. *Archives of Disease in Childhood*, **43**, 444.
- Blaese, R. M., Strober, W., Levy, A. L., and Waldmann, T. A. (1971). Hypercatabolism of IgG, IgA, IgM and albumin in the Wiskott-Aldrich syndrome. A unique disorder of serum protein metabolism. *Journal of Clinical Investigation*, **50**, 2331.
- Cawley, L. P., and Schenken, J. R. (1970). Monoclonal hypergammaglobulinemia of the γ M type in a nine-year-old girl with ataxia-telangiectasia. *American Journal of Clinical Pathology*, **54**, 790.
- Daloz, J. C., Castaing, N., Nezelof, C., and Seligmann, M. (1965). Paraprotéinémie transitoire de type γ . Observation chez un nourrisson atteint du syndrome d'Aldrich. *Presse Médicale*, **73**, 1541.
- Danon, F., Clauvel, J. P., and Seligmann, M. (1967). Les 'para-proteines' de type IgG et IgA en dehors de la maladie de Kahler. *Revue Française d'Etudes Cliniques et Biologiques*, **12**, 681.
- Danon, F., and Seligmann, M. (1972). Transient human monoclonal immunoglobulins. *Scandinavian Journal of Immunology*, **1**, 323.
- Golebiewska, H., and Rowe, D. S. (1967). Immunoglobulin G of restricted electrophoretic mobility in certain human sera. *Clinical and Experimental Immunology*, **2**, 275.
- Hallen, J. (1967). Discrete gammaglobulin (M) components in serum. *Acta Medica Scandinavica*, Suppl., **462**, 127.
- Harboe, M., Pande, H., Brandtzaeg, P., Tveter, K. J., and Hjort, P. F. (1966). Synthesis of donor type γ G-globulin following thymus transplantation in hypo- γ -globulinaemia with severe lymphocytopenia. *Scandinavian Journal of Haematology*, **3**, 351.
- Hitzig, W. H., and Jako, J. (1971). Monoclonal immunoglobulins in children. In *Protides of the Biological Fluids*, Proceedings of the 18th Colloquium. Bruges, 1970, p. 139. Ed. by H. Peeters. Pergamon Press, London.
- Hobbs, J. R. (1967). Paraproteins, benign or malignant? *British Medical Journal*, **3**, 699.
- Humphrey, J. H., Parrot, D. M. V., and East, J. (1964). Studies on globulin and antibody production in mice thymectomized at birth. *Immunology*, **7**, 419.
- Irunberry, J., Benallegue, A., Illoul, G., Timsit, G., Abbadi, M., Benabdallah, S., Boulekkine, T., Ould-Aoudia, J. P., and Colonna, P. (1970). Trois cas de maladie des chaînes alpha observés en Algérie. *Nouvelle Revue Française d'Hématologie*, **10**, 609.
- Krause, R. M. (1970). The search of antibodies with molecular uniformity. *Advances in Immunology*, **12**, 1.
- Lindqvist, K. J., Ragab, A. H., and Osterland, C. K. (1970). Paraproteinemia in a child with leukemia. *Blood*, **35**, 213.
- Loirat, C., Danon, F., and Broyer, M. (1971). Panencéphalite subaigue sclérosante survenant au cours d'un syndrome néphrotique traité par les immunosuppresseurs. *Archives Françaises de Pédiatrie*, **28**, 1083.
- Mancini, G., Carbonara, A. O., and Heremans, J. F. (1965). Immunochemical quantitation of antigens by single radial immunodiffusion. *Immunochemistry*, **2**, 235.
- Michaux, J. L., and Heremans, J. F. (1969). Thirty cases of monoclonal immunoglobulin disorders other than myeloma or macroglobulinemia. *American Journal of Medicine*, **46**, 562.
- Osserman, E. F., and Takatsuki, K. (1965). Considerations regarding the pathogenesis of the plasmacytic dyscrasias. In *Gamma Globulins*. Ed. by S. E. Bjorkman. *Series Haematologica*, **4**, 28. Munksgaard, Copenhagen.
- Osterland, C. K., Miller, E., Karakawa, W. W., and Krause, R. M. (1966). Characteristics of streptococcal group-specific antibody isolated from hyperimmune rabbits. *Journal of Experimental Medicine*, **123**, 599.
- Pierce, A. E., Chubb, R. C., and Long, P. L. (1966). The significance of the Bursa of Fabricius in relation to the synthesis of 7S and 19S immune globulins and specific antibody activity in the fowl. *Immunology*, **10**, 321.
- Radl, J., Dooren, L. J., Eijssvoegel, V. P., Vanwent, J. J., and Hijmans, W. (1972). An immunological study during post-transplantation follow-up of a case of severe combined immunodeficiency. *Clinical and Experimental Immunology*, **10**, 367.
- Radl, J., Masopust, J., Houstek, J., and Hrodek, O. (1967). Paraproteinemia and unusual dysgammaglobulinaemia in a case of Wiskott-Aldrich syndrome: an immunochemical study. *Archives of Disease in Childhood*, **42**, 608.

- Schaller, J., Davis, S. D., Ching, Y. C., Lagunoff, D., Williams, C. P. S., and Wedgwood, R. J. (1966). Hypergammaglobulinaemia, antibody deficiency, autoimmune haemolytic anaemia, and nephritis in an infant with a familial lymphopenic immune defect. *Lancet*, **2**, 825.
- Seligmann, M., Danon, F., Hurez, D., Mihaesco, E., and Preud'Homme, J. L. (1968). Alpha-chain disease: a new immunoglobulin abnormality. *Science*, **162**, 1396.
- Seligmann, M., Mihaesco, E., and Frangione, B. (1971). Studies on alpha-chain disease. *Annals of the New York Academy of Sciences*, **190**, 487.
- Stoop, J. W., Ballieux, R. E., Hijmans, W., and Zegers, B. J. M. (1971). Alpha-chain disease with involvement of the respiratory tract of a Dutch child. *Clinical and Experimental Immunology*, **9**, 625.
- Stoop, J. W., Ballieux, R. E., and Weyers, H. A. (1962). Paraproteinaemia with secondary immune globulin deficiency in an infant. *Pediatrics*, **29**, 97.
- Stoop, J. W., Zegers, B. J. M., Van Der Heiden, C., and Ballieux, R. E. (1968). Monoclonal gammopathy in a child with leukemia. *Blood*, **32**, 774.

Correspondence to Dr. M. Seligmann, Department of Immunochemistry, Research Institute on Blood Diseases, Hôpital Saint-Louis, Paris 10e, France.